PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT2004/000117	08.03.2004	02.04.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/11, A61K48/00

Applicant
GIULIANI S.P.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IT2004/000117

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V.

1 The following document is referred to in this communication:

D1: MONTELEONE G ET AL: "BLOCKING SMAD7 RESTORES TGF-BETA1 SIGNALING IN CHRONIC INFLAMMATORY BOWEL DISEASE" JOURNAL OF CLINICAL INVESTIGATION, NEW YORK, NY, US, vol. 108, no. 4, August 2001 (2001-08), pages 601-609, XP001152527 ISSN: 0021-9738

D2: US-A-6 159 697 (COWSERT LEX M ET AL) 12 December 2000 (2000-12-12)

D3: KRIEG A M: "Mechanisms and applications of immune stimulatory CpG oligodeoxynucleotides" BIOCHIMICA ET BIOPHYSICA ACTA . GENE STRUCTURE AND EXPRESSION, ELSEVIER, AMSTERDAM, NL, vol. 1489, no. 1, 10 December 1999 (1999-12-10), pages 107-116, XP004275526 ISSN: 0167-4781

D4: US 2002/034736 A1 (FALB DEAN A ET AL) 21 March 2002 (2002-03-21)

2 Novelty and inventive step

The closest prior art document D1 describes phosphorothioate oligonucleotides against Smad7 having the identical nucleotide sequence as disclosed in the present set of claims (D1 page 602, right column, lines 15-21).
The authors demonstrate that blocking Smad7 with specific antisense oligonucleotides restores TGFβ1 signalling and allows TGF-β1 to inhibit proinflammatory cytokine production by isolated mucosal lamina propria mononuclear cells. In other words Smad7 inhibition enables endogenous TGF-β to downregulate the response in IBD (inflammatory bowel disease).
In difference to the present application the nucleotide bases designated as X,Y or Z in the present application are not methylated in D1. As mentioned in the description of the present application the antisense oligonucleotides of D1 have an increased risk of undesirable side effects (page 6, lines 29-33).
The problem is thus defined as the provision of less toxic oligonucleotides blocking Smad7.
The problem is solved by the methylation of the particular nucleotides such as X,Y

(being originally CG in D1) and Z such as defined in the present set of claims.
Said solution is obvious in the light of D2, said document already suggests modified nucleobases such as 5-methylcytosine for antisense phosphorothioate oligonucleotides against Smad7 (column 40 - 42).
Therefore, the present claims are obviously derivable from the combination of D1 and D2.
In addition, D3 also suggests the methylation of CG motifs in antisense oligonucleotides, in order to have less side effects. In D4 methylphosphonate oligonucleotides against Smad7 are described (page 25, [0243 and 0245, 403]).
Therefore, the present set of claims do not involve an inventive step in view of the combination of D1 and D2 or D1, D2 and D3 or D4.